ANNALS OF SURGERY
Vol. 222, No. 4, 525–533

Mixed Reflux of Gastric and Duodenal Juices Is More Harmful to the Esophagus than Gastric Juice Alone

The Need for Surgical Therapy Re-Emphasized

Werner K. H. Kauer, M.D., Jeffrey H. Peters, M.D., Tom R. DeMeester, M.D., Adrian P. Ireland, M.D., Cedric G. Bremner, M.D., and Jeffrey A. Hagen, M.D.

From the Department of Surgery, University of Southern California School of Medicine, Los Angeles, California

Objective
The author's goal was to determine the role of duodenal components in the development of complications of gastroesophageal reflux disease.

Summary and Background Data
There is a disturbing increase in the prevalence of complications, specifically the development of Barrett's esophagus among patients with gastroesophageal reflux disease. Earlier studies using pH monitoring and aspiration techniques have shown that increased esophageal exposure to fluid with a pH above 7, that is, of potential duodenal origin, may be an important factor in this phenomenon.

Methods
The presence of duodenal content in the esophagus was studied in 53 patients with gastroesophageal reflux disease confirmed by 24-hour pH monitoring. A portable spectrophotometer (Bilitec 2000, Synectics, Inc.) with a fiberoptic probe was used to measure intraluminal bilirubin as a marker for duodenal juice in the esophagus. Normal values for bilirubin monitoring were established for 25 healthy subjects. In a subgroup of 22 patients, a custom-made program was used to correlate simultaneous pH and bilirubin absorbance readings.

Results
Fifty-eight percent of patients were found to have increased esophageal exposure to gastric and duodenal juices. The degree of mucosal damage increased when duodenal juice was refluxed into the esophagus, in that patients with Barrett's metaplasia (n = 27) had a significantly higher prevalence of abnormal esophageal bilirubin exposure than did those with erosive esophagitis (n = 10) or with no injury (n = 16). They also had a greater esophageal bilirubin exposure compared with patients without Barrett's changes, with or without esophagitis. The correlation of pH and bilirubin monitoring showed that the majority (87%) of esophageal bilirubin exposure occurred when the pH of the esophagus was between 4 and 7.

Conclusions
Reflux of duodenal juice in gastroesophageal reflux disease is more common than pH studies alone would suggest. The combined reflux of gastric and duodenal juices causes severe

esophageal mucosal damage. The vast majority of duodenal reflux occurs at a pH range of 4 to 7, at which bile acids, the major component of duodenal juice, are capable of damaging the esophageal mucosa.

Clinical observation as well as studies of the natural history of gastroesophageal reflux disease has shown that approximately 25% of patients have a course characterized by recurrent progressive mucosal damage. This can occur despite medical therapy.[1] Furthermore, a disturbing increase in the prevalence of Barrett's esophagus and esophageal adenocarcinoma has been noted in Western countries.[2,3] This high-risk group of patients is distinguished by a high prevalence of a mechanically defective lower esophageal sphincter and increased esophageal exposure to fluid with a pH below 4 and above 7.[4] Further, detailed studies of esophageal pH exposure have shown that the occurrence of mucosal injury correlates with exposure time to fluid, with a pH below 2 and above 7.[5] These observations suggest a synergistic role of gastric and duodenal juices in the development of esophageal mucosal injury.

Although the interaction of gastric juice, duodenal juice, and luminal pH on the development of mucosal damage have been studied in animals, it has not been possible to do so in patients.[6,7] It has been shown is previous studies that duodenal content can be aspirated from the esophagus of patients with gastroesophageal reflux disease and that its presence is related to mucosal injury.[8,9] In the current study we expanded these observations by monitoring esophageal pH and bilirubin exposure over 24 hours in patients with gastroesophageal reflux disease an ambulatory mode and observed the relationship between gastric juice (identified by a drop in esophageal pH < 4) and duodenal juice (identified by the presence of bilirubin) to mucosal injury.

PATIENTS AND METHODS

Study Population

The study population consisted of 25 healthy subjects (male-to-female ratio, 19:6; median age, 31 years; range, 19–42 years) and 53 patients (male-to-female ratio, 31:22; median age, 47.5 years; range, 20–78 years) with gastroesophageal reflux disease. All subjects had standard esophageal manometry to identify the location of the lower esophageal sphincter and 24-hour pH and bilirubin monitoring to quantify esophageal exposure to gastric and duodenal juices. All patients had undergone previous upper gastrointestinal endoscopy. No patients had previous esophageal or gastric surgery.

In a subgroup of 22 patients with a positive acid score on pH monitoring, simultaneous monitoring of esophageal pH and bilirubin contents was performed. A comparison of pH and absorbance readings for each reflux event was performed by means of a specifically developed computer program.

Endoscopy

Upper gastrointestinal endoscopy was performed in all patients, and the findings were classified as "no mucosal injury" (n = 16), "erosive esophagitis" (n = 10), and "Barrett's esophagus" (n = 27). Barrett's metaplasia was defined by the presence of specialized intestinal metaplasia on biopsy taken above the gastroesophageal junction.

Ambulatory 24-Hour Esophageal pH and Bilirubin Monitoring

A glass esophageal pH probe and a fiberoptic probe to detect bilirubin were passed through the nose and positioned 5 cm above the upper border of the lower esophageal sphincter. Esophageal pH was recorded on a portable digital data recorder and analyzed as described previously.[10] Bilirubin absorbance was measured and recorded by a portable optoelectronic data logger capable of directly measuring bilirubin by spectrophotometry, based on the specific light absorption of bilirubin at a wavelength of 453 nm. This technique has been described previously.[11] Figure 1 shows the cumulative descending frequency distribution of 24-hour bilirubin exposure at distinct threshold values for absorbance. An absorbance threshold of 0.2 was selected because at this level less than 5% of healthy subjects had bilirubin detected in their esophagus. The fiberoptic probe was calibrated in water before and after monitoring. Records with a bilirubin absorbance drift greater than 0.15 were discarded.

Medications were discontinued 48 hours before testing, except for omeprazole, which was discontinued at least 2 weeks earlier. With monitors in place, the patient was sent home and instructed to remain in an upright or seated position until retiring for the night and to follow a special diet, which involved restriction to three meals a day composed of food with a pH between 5 and 7 and

Presented at the 115th Annual Meeting of the American Surgical Association, April 6–8, 1995, Chicago, Illinois.
Address reprint requests to Jeffrey H. Peters, M.D., University of Southern California School of Medicine, Department of Surgery, 1510 San Pablo Street, Suite 514, Los Angeles, CA 90033-4612.
Accepted for publication April 10, 1995.

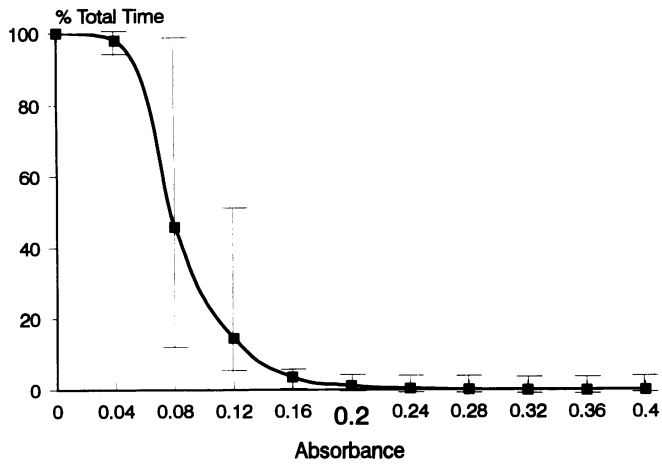

Figure 1. Cumulative descending frequency distribution graph of the prevalence of total study time in which bilirubin was detected above distinct absorbance thresholds in 25 healthy subjects. Data are plotted as medians with the 25th and 75th percentiles. Based on this curve, the threshold absorbance of 0.2 was chosen as an indicator of the presence of bile in the esophageal lumen.

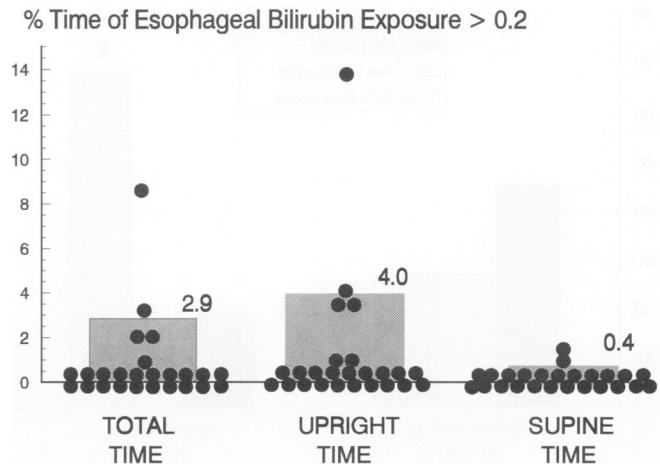

Figure 2. Percentage time of esophageal bilirubin exposure in 25 healthy subjects for the total upright and supine time periods of a 24-hour study. The shaded area represents the normal range (95th percentile, upper limit of normal).

free of foods with a high bilirubin absorbance.[11] A diary was kept of food and fluid intake, symptoms, and the time of the supine and upright positions. Twenty-four-hour pH and bilirubin absorbance data were analyzed with a commercially available software program (Gastrosoft, Inc., Dallas, Texas).

Definition of Reflux Types

Patients with increased esophageal exposure to pH below 4 but with absence of bilirubin exposure were classified as having gastric reflux. Patients with increased esophageal exposure to pH below 4 and bilirubin were classified as having mixed reflux.

Statistics

Prevalence data were compared between groups using Fisher's exact test. The Mann–Whitney *U* test was used to compare continuous data between groups. A probability value of less than 0.05 was considered significant. Unless otherwise stated, all data are expressed as medians.

RESULTS

Prevalence of Esophageal Bilirubin Exposure

Esophageal bilirubin exposure was studied in 25 healthy subjects, all of whom were asymptomatic and had normal 24-hour ambulatory esophageal pH studies to exclude the presence of pathologic acid reflux. For each subject, the percentage time of bilirubin exposure was plotted for total, upright, and supine time periods. The median and 95th percentile values were determined for the group. The median percentage time of esophageal bilirubin exposure over a 24-hour period in healthy subjects was 0.1% and the 95th percentile value was 2.9%. The upright and supine exposure values differed slightly, with a 95th percentile of 4.0% and 0.4%, respectively (Fig. 2). Values above the 95th percentile level among healthy subjects for the total 24-hour period were used to identify increased esophageal exposure to duodenal juice in 53 patients with foregut symptoms and increased esophageal acid exposure on pH monitoring. Twenty-two of these patients had increased esophageal exposure

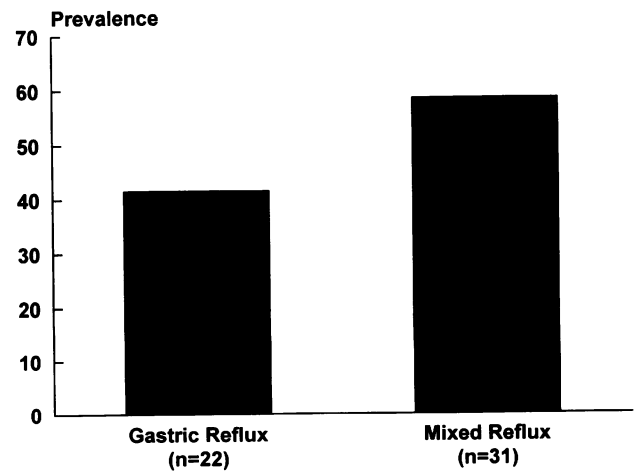

Figure 3. Prevalence of reflux types in 53 patients with gastroesophageal reflux disease.

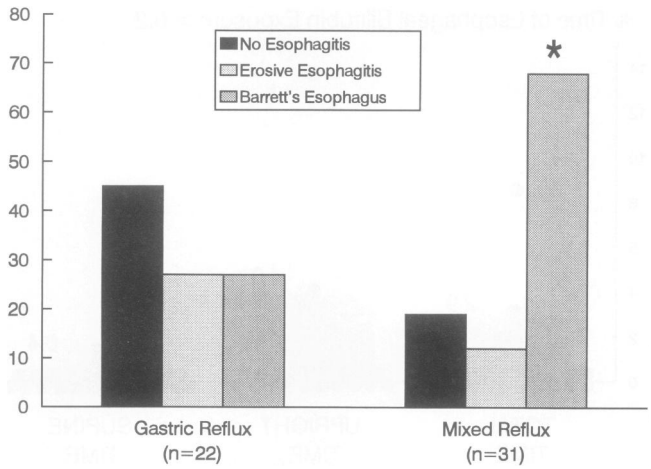

Figure 4. Prevalence of mucosal injury in patients with reflux of gastric juice only (gastric reflux) and in those with reflux of combined gastric and duodenal juices (mixed reflux) (*p < 0.005 *vs.* gastric reflux).

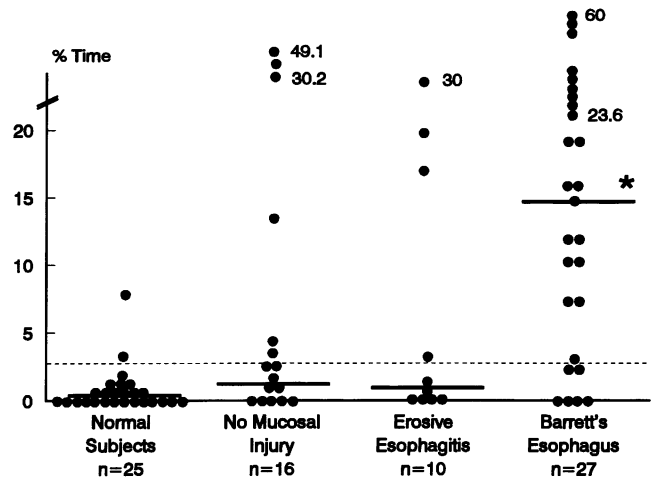

Figure 6. Duration of esophageal bilirubin exposure in healthy subjects and in patients with gastroesophageal reflux disease with varied degrees of mucosal injury (*p < 0.05 *vs.* all other groups).

to acid only (gastric reflux), whereas the remaining 31 had increased esophageal exposure to acid and bilirubin (mixed duodenogastric reflux) (Fig. 3).

Relationship of Bilirubin Exposure to Mucosal Injury

Of the 53 patients with gastroesophageal reflux, 16 had no endoscopic evidence of mucosal injury, 10 had endoscopic evidence of erosive esophagitis, and 27 demonstrated Barrett's metaplastic changes. Patients in whom there was a reflux of gastric and duodenal juices had mucosal injury of greater severity than those who experienced reflux of gastric juice only, in that Barrett's metaplasia occurred in 6 of 22 (27%) of the former and 21 of 31 (68%, $p < 0.005$) of the latter (Fig. 4). Further, patients with Barrett's metaplasia had a significantly higher prevalence of abnormal esophageal bilirubin exposure than did those with esophagitis or no injury (Fig. 5). The latter two groups differed significantly compared with healthy subjects but not from each other. Patients with Barrett's esophagus also had a greater duration of esophageal bilirubin exposure compared with patients with esophagitis or no mucosal injury (Fig. 6).

Patterns of Esophageal Bilirubin Exposure

Twenty-two patients underwent simultaneous bilirubin and 24-hour pH monitoring. A custom software program, capable of performing a moment-to-moment comparison of esophageal pH and bilirubin presence, was used to investigate the relationships of pH and bili-

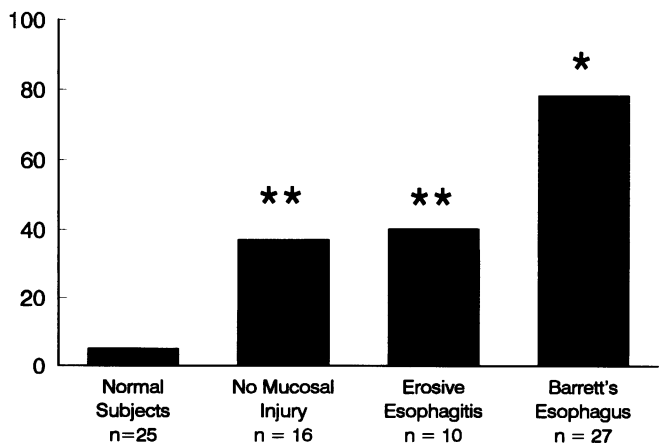

Figure 5. Prevalence of abnormal esophageal bilirubin exposure in healthy subjects and in patients with gastroesophageal reflux disease with varied degrees of mucosal injury (*p < 0.03 *vs.* all other groups, **p < 0.03 *vs.* healthy subjects).

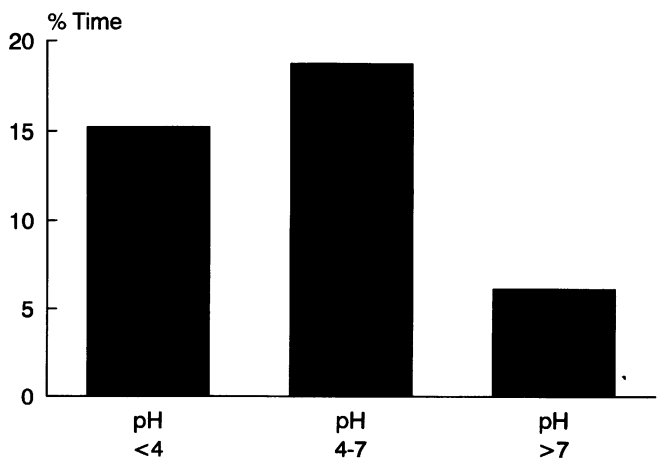

Figure 7. Duration of bilirubin exposure during esophageal pH intervals below 4, between 4 and 7, and above 7.

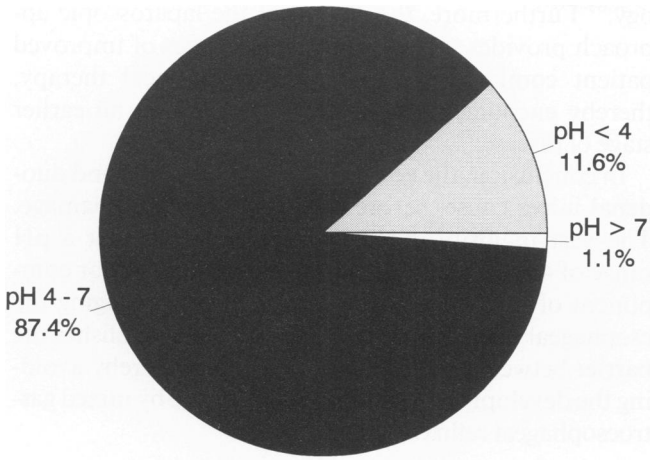

Figure 8. Esophageal luminal pH during bilirubin exposure.

rubin exposure. Figure 7 shows the percentage time of esophageal bilirubin exposure when the esophageal pH was below 4, between 4 and 7, and above 7. No significant difference in the pattern of exposure at these pH intervals was seen among the patients with varied mucosal injury, although those with Barrett's esophagus had higher esophageal bilirubin exposure at the pH range of 4 to 7. Results of all patients, however, were significantly different from healthy subjects. Analysis of simultaneous pH and bilirubin monitoring showed that the majority of esophageal bilirubin exposure occurred in the pH range of 4 to 7 (Fig. 8). Twenty-nine percent of reflux episodes could be classified as containing gastric juice only (pH < 4 and bilirubin absorbance < 0.2), 64% contained potentially a mixture of gastric juice buffered by duodenal juice (pH < 7 and bilirubin absorbance > 0.2), and only 1% contained duodenal juice potentially free of gastric juice (pH > 7 and bilirubin absorbance > 0.2) (Fig. 9).

DISCUSSION

We have shown that patients with reflux of gastric juice have less severe mucosal injury than those with reflux of gastric and duodenal juices. Further, patients with Barrett's esophagus have a significantly higher prevalence of increased exposure to duodenal juice than patients with erosive esophagitis or with no mucosal injury. The mean percentage time of esophageal exposure to duodenal juice was also significantly higher in patients with Barrett's esophagus. Simultaneous pH and bilirubin monitoring showed that esophageal exposure to duodenal juice occurs at all pH values. In patients with gastroesophageal reflux disease, duodenal content was detected within the esophagus 15% of the time when the pH was below 4, 19% of the time when the pH was between 4 and 7, and 6% of the time when the pH was above 7. An analysis of the cumulative period during which the esophagus was exposed to duodenal juice showed that the pH of the esophagus was between 4 and 7 87% of the time. This pH is considered normal for the esophagus; consequently, such reflux goes undetected and unappreciated when analyzed by traditional criteria.

The clinical implication of these findings is that alterations in the gastric pH environment caused by acid suppression therapy may allow the reflux of gastric juice containing soluble bile salts and active duodenal enzymes, which may potentiate esophageal injury and encourage metaplasia. These possibilities should be considered in view of the fact that antireflux surgery is the only means available for prevention of esophageal exposure to gastric and duodenal juices.

The results of the current study encourage further study of the importance of bile salts in the development of complications of gastroesophageal reflux disease. A considerable body of experimental evidence indicates that maximal epithelial injury occurs during exposure to bile salts combined with acid and pepsin.[6,9,12-21] For bile acids to injure mucosal cells, they must be soluble and unionized, so that the unionized nonpolar form may enter mucosal cells.[22,23] Before secretion into bile, 98% of bile acids are conjugated with either taurine or glycine in a ratio of about 3:1. Conjugation increases the solubility and ionization of bile acids by lowering their pK_a.[24] At the normal duodenal pH of approximately 7, greater than 90% of bile salts are in solution and completely ionized. At pH ranges of 2 to 7, a mixture of the ionized salt and the lipophilic, nonionized acid is present.[25] Acidification of bile to below pH 2 results in an irreversible bile acid precipitation.[26] Consequently, under normal physi-

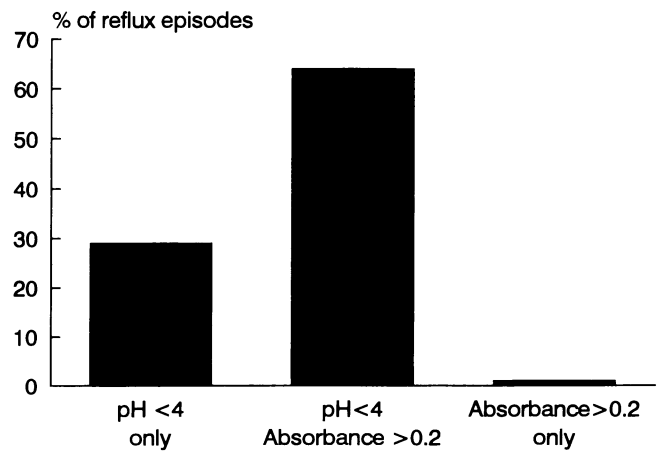

Figure 9. Duration of reflux events containing acid only (pH < 4), acid and bilirubin (pH < 4 and absorbance > 0.2), and bilirubin only (absorbance > 0.2) when pH and bile probes were analyzed simultaneously for moment-to-moment exposure.

ologic conditions, bile acids precipitate and are of minimal effect when an acidic gastric environment exists. Conversely, in a more alkaline gastric environment, such as after gastrectomy or with acid suppression therapy, bile salts remain in solution, are partially dissociated, and, when refluxed into the esophagus, can cause severe mucosal injury by crossing the cell membrane and damaging the mitochondria.[27,28]

This hypothesis is supported by clinical evidence showing that complications of gastroesophageal reflux, such as esophagitis, stricture, and Barrett's metaplasia, occur in the presence of two predisposing factors: a mechanically defective lower esophageal sphincter and an increased esophageal exposure to fluid with a pH of below 4 and above 7.[4] The duodenal origin of esophageal contents in patients with an increased exposure to a pH above 7 has been confirmed by esophageal aspiration studies.[8] In the current study we have clarified and expanded these observations by measuring esophageal bilirubin exposure over a 24-hour period as a marker for the presence of duodenal juice. This technology, although not a quantitative measurement of bilirubin,[29] showed that 58% of the patients with gastroesophageal reflux disease had increased esophageal exposure to duodenal juice, that this exposure occurs most commonly when the esophageal pH is between 4 and 7, and that it is associated with a more severe mucosal injury.

The possibility that the combination of refluxed gastric and duodenal juices is more noxious to the esophageal mucosa than gastric juice alone may explain the repeated observation that 25% of patients with reflux esophagitis developed recurrent and progressive mucosal damage, often despite medical therapy.[1,30,31] A potential reason is that acid suppression therapy is unable to consistently maintain the pH of refluxed gastric and duodenal juices above 7. Lapses into pH ranges from 2 to 7 encourage the formation of undissociated, nonpolarized solubility of bile acids that can damage the mucosa. For bile acids to remain completely ionized in their polarized form, and thus innocuous, the pH of the refluxed material must be maintained above 7, 24 hours a day, 7 days a week, for the patient's lifetime. In practice, this is not only impractical, but likely impossible, unless very high doses of medications are used.[32] The use of lesser doses may allow esophageal mucosal damage to occur while the patient is relatively asymptomatic.[33] Consequently, the development of recurrent progressive disease while receiving medical therapy can occur. In contrast, antireflux surgery has been shown to be highly effective, safe, and durable.[34] In addition, antireflux surgery prevents the reflux of gastric and duodenal juices. The selection of the appropriate antireflux procedure will result in an excellent clinical outcome for nearly all patients, regardless of the severity of their altered esophageal physiology.[35] Furthermore, the advent of the laparoscopic approach provides the additional advantages of improved patient comfort and acceptance of surgical therapy, thereby encouraging surgical intervention at an earlier stage of disease.[36,37]

In conclusion, the combined reflux of gastric and duodenal juices causes severe esophageal mucosal damage. The vast majority of duodenal reflux occurs at a pH range of 4 to 7, a pH at which bile acids, the major component of duodenal juice, are capable of damaging the esophageal mucosa. Antireflux surgery re-establishes the barrier between stomach and esophagus, thereby avoiding the development of esophageal damage by mixed gastroesophageal reflux.

References

1. Monnier Ph, Ollyo JB, Fontolliet C, et al. Epidemiology and natural history of reflux esophagitis. Semin Laparoscop Surg 1995; 2(1): 2–9.
2. Levine DS. Barrett's esophagus. Sci Am Sci Med 1994; 1:16–25.
3. Para M, Cameron AJ, Trastek VF, et al. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology 1993; 104:510–513.
4. Stein HJ, Barlow AP, DeMeester TR, et al. Complications of gastroesophageal reflux disease: role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. Ann Surg 1992; 216:35–43.
5. Bremner RM, Crookes PF, DeMeester TR, et al. Concentration of refluxed acid and esophageal mucosal injury. Am J Surg 1992; 164(5):522–527.
6. Gillison EW, DeCastro VAM, Nyhus CT, et al. The significance of bile in reflux esophagitis. Surg Gynecol Obstet 1972; 134: 419–424.
7. Stoker DL, Williams JG. Alkaline reflux esophagitis. Gut 1991; 32: 1090–1092
8. Stein HJ, Feussner H, Kauer W, et al. Alkaline gastroesophageal reflux: assessment by ambulatory esophageal aspiration and pH monitoring. Am J Surg 1994; 167:163–168.
9. Iftakhar SY, Ledingham S, Steele RJC, et al. Bile reflux in columnar lined Barrett's oesophagus. Ann Roy Coll Surg Engl 1993; 75: 411–416.
10. Jamieson JR, Stein HJ, DeMeester TR, et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992; 87:1102-1111.
11. Kauer WKH, Burdiles P, Ireland AP, et al. Does duodenal juice reflux into the esophagus of patients with complicated GERD? Evaluation of a fiberoptic sensor for bilirubin. Am J Surg 1995; 169:98–104.
12. Gotley DC, Morgan AP, Cooper MJ. Bile acid concentrations in the refluxate of patients with reflux oesophagitis. Br J Surg 1988; 75:587–590.
13. Harmon JW, Johnson LF, Maydonovitch CL. Effect of acid and bile salts in the rabbit esophageal mucosa. Dig Dis Sci 1981; 26:65–72.9.
14. Lillimoe KD, Gadacz TR, Harmon JW. Bile absorption occurs during disruption of the esophageal mucosal barrier. J Surg Res 1983; 35:57–62.
15. Lillimoe KD, Johnson LF, Harmon JW. Role of the components of the gastroduodenal contents in experimental acid esophagitis. Surgery 1982; 92:276–284.

16. Lillimoe KD, Johnson LF, Harmon JW. Alkaline esophagitis: a comparison of the ability of components of gastroduodenal contents to injure the rabbit esophagus. Gastroenterology 1983; 85:621–628.
17. Moffat RC, Berkas EM. Bile esophagitis. Arch Surg 1965; 91:963–965.
18. Salo JA, Kivilaakso E. Role of bile salts and trypsin in the pathogenesis of experimental alkaline esophagitis. Surgery 1983; 93: 525–532.35.
19. Kivilaakso E, Fromm D, Silen W. Effect of bile salts and related compounds on isolated esophageal mucosa. Surgery 1980; 87:280–285.
20. Lillimoe KD, Johnson LF, Harmon JW. Taurodeoxycholate modulates the effects of pepsin and trypsin in experimental esophagitis. Surgery 1985; 97:662–667.
21. Schweitzer EJ, Harmon JW, Bass BL, Batzri S. Bile acid reflux precedes mucosal barrier disruption in the rabbit esophagus. Am J Physiol 1984; 247:G480–G485.
22. Schweitzer EJ, Bass BL, Batzri S, Harmon JW. Bile acid accumulation by rabbit esophageal mucosa. Dig Dis Science 1986; 31: 1105–1113.
23. Harmon JW, Bass BL, Batzri S. Alkaline reflux gastritis; Mechanism of injury. Probl Gen Surg 1993; 10:201–206.
24. Heaton KW. Bile salts. *In* Wright R, Alberti KGMM, Karran S, et al., eds. Liver and Biliary Disease. London: WB Saunders; 1979: 233–254.
25. Small DM. The physical chemistry of cholanic acids. *In* Nair PP, Kritchevsky, D eds. The Bile Acids: Chemistry, Physiology and Metabolism. Vol 1. New York: Plenum Press; 1971: 249–356.
26. Barthlen W, Liebermann-Meffert D, Feussner H, et al. Influence of pH on bile acid concentration in human, pig and commercial bile: implications for 'alkaline' gastro-esophageal reflux. Dis Esoph 1994; 7:127–130.
27. Krahenbuhl S, Talos C, Fischer S, Reichen J. Toxicity of the bile acids on the electron transport chain of isolated rat liver mitochondria. Hepatology 1994; 19:471–479.
28. Spivey JR, Bronk SF, Gores GJ. Glycochenodeoxycholate induced lethal cell injury in rat hepatocytes. J Clin Invest 1993; 92:17–24.
29. Ostrow JD. Bilitec to quantitate duodenogastric reflux: is it valid? Gastroenterology 1995; 108:1332–1334.
30. Sontag SJ, Hirschowitz BI, Holt S, et al. Two doses of omeprazole versus placebo in symptomatic erosive esophagitis: the U.S. multicenter study. Gastroenterology 1992; 102: 119–128.
31. Champion G, Richter JE, Vaezi MF, et al. Duodeno-gastroesophageal reflux: relationship to pH and importance in Barrett's esophagus. Gastroenterology 1994; 107:747–754.
32. Klinkenberg-Knol EC, Festen HPM, Jansen JBMJ, et al. Long-term treatment with omeprazole for refractory reflux oesophagitis: efficacy and safety. Ann Intern Med 1994; 121:161–167.
33. Brossard E, Ollyo JB, Monnier PH, et al. Columnar-type epithelium (Barrett's epithelium) develops after healing in 18% of adults with erosive esophagitis or ulcerative reflux esophagitis. Gastroenterology 1991; 100(5):A36.
34. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease: evaluation of primary repair in 100 consecutive patients. Ann Surg 1986; 204:9–20.
35. Kauer WKH, Peters JH, Ireland AP, et al. A tailored approach to antireflux surgery. J Cardiovasc Thorac Surg 1995; 109:1–7.
36. Hinder RA, Filipi CJ, Wetscher G, et al. Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease. Ann Surg 1994; 220: 472–483.
37. Peters JH, Heimbucher J, Kauer WKH, et al. Clinical and physiologic comparison of laparoscopic and open Nissen fundoplication. J Am Coll Surg 1995; 180:385–393.

Discussion

PROFESSOR ALAN G. JOHNSON (Sheffield, England): This is a very important paper. It has drawn attention again to a phenomenon that was observed 25 years ago by Walford Gillison when he was working with LLoyd Nyhus here in Chicago, but we have not had a good way to measure it in patients before now.

In our unit, we are using a sodium ion selective electrode, which detects both pancreatic and bilirubin and bile (*i.e.*, the total duodenal juice) and we are finding similar results. We feel that the pancreatic juice may be as important as bile in damage, but the sodium method does require suppression of acid to prevent interference by hydrogen ions.

Did you analyze the symptoms? I have the suspicion that we may reduce the symptoms by blocking the acid but not the damage from duodenal juice. I wonder if you have found any difference in the symptoms between those who have duodenal, mixed, or pure acid reflux?

For the gastric mucosa, the pH of bile salts is important in damage production, and this may also apply to the esophagus when the mixed reflux may be more damaging than either acid or duodenal reflux alone. Indeed, alternate reflux of acid and duodenal juice may be more damaging than a mixture.

You mentioned that the only method we have to prevent duodenal reflux is surgery. However, prokinetic drugs, such as cisapride, reduce reflux and enhance esophageal clearance, and we often use a combination of an acid blocking drug and cisapride. There is evidence that the combination heals esophagitis more effectively than acid production alone, which supports what you have been saying in your paper.

I think we should no longer talk about "alkaline reflux." Your group originally used this term because you were measuring pH as the criterion of duodenal juice reflux. Now, we can refer to duodenal juice reflux, bile reflux, or acid reflux respectively. I agree with you that we may be storing up a problem for the future by just thinking of blocking acid, and this is a very important paper because it draws our attention to the reflux of other damaging substances.

DR. J. RUDIGER SIEWERT (Munchen, Germany): I enjoyed very much discussing this very interesting, very important paper. From my point of view, this paper is important on three aspects.

First, it stops the so-called alkaline reflux story, at least in patients with primary reflux disease and particularly without previous gastric surgery, because it is shows very nicely that it is not only the pH of the reflux but the contents of the reflux. Duodenal juice can be found at nearly any pH.

Second, it gives, from the theoretical point of view, an explanation why we see no response in our curative treatment in approximately 15% to 20% of our patients. Moreover, it opens a new indication for surgery that makes surgery more attractive in patients with duodenal reflux.

Third, it shows that duodenal reflux is much more frequent in patients with Barrett-esophagus. This brings us to the question: Is the duodenal reflux the cause, or at least an important precondition of Barrett-metaplasia? If so, is there also a connection with the frequent malignant degeneration?